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Carrier Testing in the Fragile X Syndrome: Attitudes and Opinions of Obligate Carriers

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This study surveyed obligate carriers of the fragile X syndrome fra(X) to ascertain opinions and attitudes regarding carrier testing. Female carriers of fra(X) syndrome were recruited during their visits to the Fragile X Clinic at Duke University Medical Center. Twenty-eight obligate carriers completed a 48 question structured interview and a visual analog scale (VAS). Strong trends in the responses were identified. Fra(X) syndrome was viewed as a very serious problem and the risk to offspring high. Subjects reported that prior knowledge of carrier status would have changed their reproductive plans. All felt that relatives should be informed about the inheritance of fra(X) syndrome; the mean age given for preferred age to inform their children of the inheritance of fra(X) syndrome was 12 years, and mean age given for optimal timing of carrier testing was 10 years. The women interviewed indicated that growing up with knowledge of their carrier status would have been preferable to learning this information as adults and they endorsed an aggressive approach to informing and testing their children. Further investigation is warranted to determine the psychological consequences of carrier testing for fra(X) syndrome in order to develop appropriate guidelines for testing and informing individuals at risk for fra(X) syndrome. Am. J. Med. Genet 68:62–69, 1997

KEY WORDS: fragile X syndrome; carrier testing; genetic counseling

INTRODUCTION

Fragile X syndrome (fra(X)) is a common inherited condition causing mental retardation [Brown and Jenkins, 1992]. The discovery of the fra(X) gene, known as FMR-1, in 1991 led to the development of improved testing for both carriers and affected individuals [Heitz et al., 1991; Kremer et al., 1991; Oberlé et al., 1991; Yu et al., 1991; Bell et al., 1991; Fu et al., 1991]. Prior to the development of a DNA based test, diagnosing fra(X) syndrome and carrier testing was difficult and often indeterminate. Although DNA based testing allows for accurate diagnosis and carrier determination, many questions regarding the impact and the optimal timing for carrier testing and notification of DNA test results remain unanswered.

Very little information is known regarding the attitudes of carriers for X-linked disorders about timing for testing and feelings related to being a carrier. Prior studies of carriers of X-linked conditions have been limited to evaluating the degree to which available resources have been utilized, such as the use of prenatal diagnosis in pregnancies at risk, attitudes regarding abortion, and the percentage of those at risk who choose carrier testing [Miller et al., 1987; Kraus and Brettler, 1988; Meryash, 1992; Meryash and Abuelo, 1988; Beeson and Golbus, 1985; Costakos et al., 1991; Varekamp et al., 1990, 1992]. The purpose of this study was to ascertain the attitudes and opinions of obligate carriers regarding these issues and the impact that fra(X) syndrome has had on their personal and family relationships.

MATERIALS AND METHODS

Study Sample/Demographics

Twenty-eight female carriers of the fra(X) were recruited through the Fragile X Clinic at Duke University Medical Center. All women had undergone genetic counseling prior to completing the measures and all knew that they were carriers of the fra(X) syndrome. A wide range of women of variable backgrounds were included (Table I). Women were recruited into the study as they were encountered.

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TABLE I. Demographics of Study Participants

Premutation carriers	25	
Full mutation carriers	3	
Age	Mean 41.78 years (SD 11.8)	Range (23–72 years)
Number of children	Mean 2.28 (SD 0.8)	Range (0–4)
Years married	Mean 18 years	Range <1–38 years
Years since diagnosis	Mean 5.9 years (SD 4.6)	Range 0–16 years
Education	2 < high school 8 high school graduates 13 college or technical 5 postgraduate	
Hours employed outside the home	Mean 30 hours	
Learned about fragile X through child's diagnosis	61% (17/28)	
Learned through a relative	39% (11/28)	

Measurements

A structured interview and visual analog scale, developed for use in this study, was completed by 28 carriers of the fra(X) syndrome. The structured interview included 48 open and closed ended questions. Questions were asked regarding demographics, understanding of the genetics of fra(X) syndrome, family planning issues including prenatal diagnosis, opinions regarding timing for carrier testing, how relatives should be told of genetic risk, and marital and family relationships. The questions regarding preferred age for carrier testing and informing of carrier status for themselves, their children, and relatives were asked in several different formats to ensure understanding and to allow for clarification. The various questions asked were either open ended or with multiple choices grouped either by age or an age commonality such as school. Follow-up questions were asked to ascertain why a specific response was given.

The 11 item visual analog scale (VAS) repeated many key questions asked in the structured interview, allowing for a scaled numeric response. The VAS has been used as a graphic method to quantify sensations such as well being and is accepted as a good estimator of the intensity of physical and emotional pain [Carlsson, 1983; Vogelsand, 1988; Bond and Lader, 1974]. As the VAS measures an infinite number of points between extremes the scores tend to be evenly distributed along the continuum rather than being grouped around the descriptive word. The scale is scored by measuring millimeters from the end of the line to the subject's mark. The scale ranges from a 1 (indicating very upset, not very well, or a very serious problem) to 10 (indicating not upset, very well, or not a problem).

Statistical Analysis

The main statistical objective of this study was to quantify responses regarding the optimal age to be notified of the inheritance, to have carrier testing done, and to determine perceived changes in personal and family relationships brought about by knowledge of carrier status for fra(X) syndrome. Different types of data were collected from the study sample, including demographics, the responses from open and closed ended questions from the structured interview, and continuous numeric values from the visual analog scale. The data were entered into a data base and imported into PC-SAS version 6.10 data set for analysis. Descriptive univariant analysis was performed on numeric variables of interest. For variables related to specific study questions (age at notification of carrier status and age at which offspring should be notified), the continuous responses were dichotomized using the median value to maximize cell size. The frequency counts of these variables were then used to stratify other dichotomous variables obtained from the structured interview or mean responses from questions on the visual analog scale. Frequency counts in each stratum were then tested for relationships using Fisher's Exact test in the case of 2×2 frequency tables or Students t-test for differences between means. Because of the small number of full mutation carriers, it was not possible to analyze the data by full vs. premutation carriers.

RESULTS

Genetic Risk

The women interviewed viewed fra(X) as a very serious problem with a mean on the VAS of 1.2 (SD 1.9) (Table II). When asked "How are your children with fra(X) doing," they responded with a mean of 5.6 (SD 2.33). The mean was 5.9 (SD 2.03) for doing better than they had anticipated based on the diagnosis of fra(X) syndrome. Although only three of the women are carriers of the full mutation, 32% (9/28) felt that they had some emotional or learning problems which resulted from being a carrier.

These women felt that their chances of having or having had a child with fra(X) syndrome was high with a mean on the VAS of 7.66 (SD 2.37). When asked if they felt their risk was high, medium, or low for having an affected son, 57% (16/28) responded as high, 39.3% (11/28) medium, and only 3.6% (1/28) low. When asked for a numerical risk assessment for the chance of having an affected son, the mean response was 54.4% (SD 21.07), with two women responding that their risk was 100%. Overall, subjects viewed their risk for having an affected daughter as slightly lower; 25% (7/28) as high, 53.6% (15/28) as medium, and 21% (6/28) as low. The

TABLE II. Results of Visual Analog Scale

Questions (abbreviated)	Range 1–10*
1. Chance of having an affected child?	7.66 (SD 2.37)
2. How serious a problem?	1.2 (SD 1.9)
3. How is the affected child doing?	5.6 (SD 2.33)
4. Affected child better or worse than expected?	5.9 (SD 2.03)
4. How upsetting for family?	4.3 (SD 2.75)
5. Changed relationship with spouse?	5.7 (SD 2.35)
6. Changed relationship with siblings?	6.4 (SD 1.69)
7. Changed relationship with relatives?	5.57 (SD 1.70)
8. Changed way feel about self?	5.01 (SD 2.3)
9. How felt when first found out carrier for fra(X)?	4.99 (SD 3.13)
10. How feel now about carrier status?	6.8 (SD 2.70)

* The scale ranges from 1 (indicating very upset, not very well, very serious problem) to a 10 (indicating not upset, very well, not a problem).

mean numeric response given was 49.05% (SD 15.38) (Fig. 1).

Sixty-seven percent (19/28) felt that knowing about fra(X) syndrome had changed their plans about having more children and said that they were not having any more because of the risk. Those who stated it had not change their plans indicated that their families were complete at the time of learning the diagnosis. Eighty-nine percent (25/28) felt that if they had known that fra(X) syndrome was in their families prior to having children they would have either reduced the size of their families or not have had any biological children. Eighty-two percent (23/28) said they would have used prenatal diagnosis if it had been available to them to either prevent the birth of an affected child or to help them prepare for what may happen.

Feelings Related to Being a Fra(X) Syndrome Carrier

Sixty-seven percent (19/28) said that learning they were carriers of fra(X) had changed they way they viewed themselves with a mean on the VAS of 5.01 (SD 2.4). Of those, 52.6% (10/19) indicated a positive change with 47.3% (9/19) feeling the change was negative. For those who felt the change was negative the responses indicated that this change was based either on having had an affected child and/or feelings of being abnormal or inferior. Statements such as the following were common: "I hate being a carrier because my children are affected," "I'm not as normal as I thought I was," or "I feel guilty about what my affected child is unable to do." The women responding with a positive

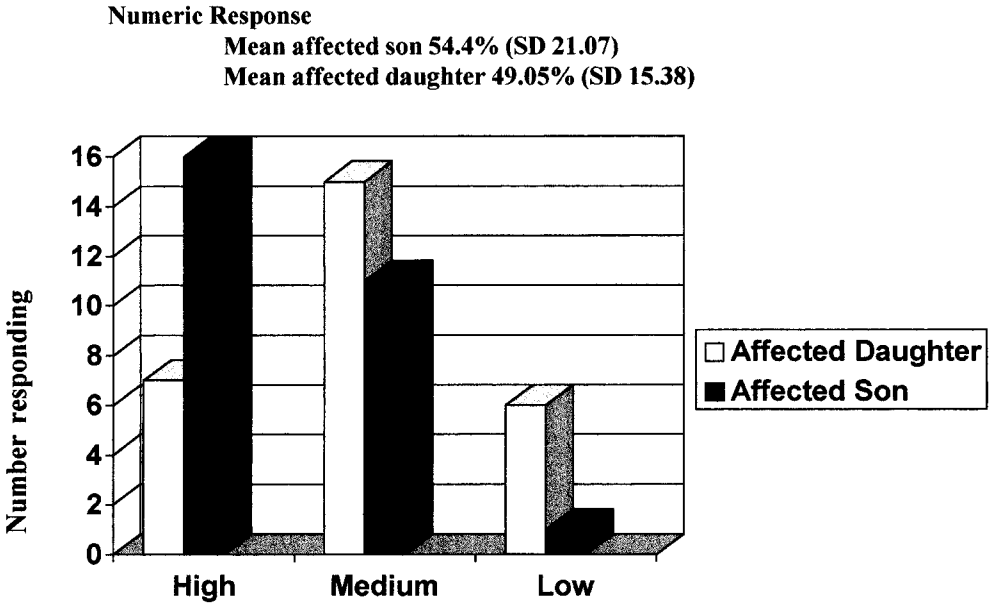

Fig. 1. Perceived risk of having an affected child.

change indicated an improved sense of self awareness and understanding.

Subjects reported that over time there was a lessening in the intensity of the negative feelings associated with first learning they were carriers. When asked how they felt when they initially found out they were carriers, a mean of 4.19 (SD 3.13) on the VAS was given. Eleven of the women (39%) responded with a one, indicating the most upsetting choice on the scale. On the follow-up question of "How do you feel now?", only one women responded with a score of one and the mean increased to 6.8 (SD 2.70). A common response was: "At first I felt inferior, then I realized I didn't do anything to cause it (fra(X)) and wasn't at fault." Eighty-seven percent indicated they did not feel guilty about being a carrier. However, they stated they were sometimes angry or depressed and would change their carrier status if they could. Their responses also indicated that there was emotional relief in finding out the cause of the mental retardation in the family.

Attitude About Timing of Carrier Testing

All of the women stated that they wished they had learned this information earlier than they did. When asked if they felt it would be an advantage, disadvantage, or neither, at various grouped ages to have learned they were carriers, 60% (17/28) felt it would have been an advantage by age 12–15 years and 92.9% (26/28) felt it would have been an advantage by the age of 16–18 years of age. The mean age indicated that they themselves wished they had first learned that fra(X) syndrome was in their families and they had a risk for having affected children was 16.21 years (SD 4.34). When asked at what age they would liked to have known they were carriers, the age indicated was a slightly younger mean of 15.03 years (SD 5.78). When asked the question as it specifically related to school (preschool, elementary, middle, and high school), 75% (21/28) wished they had known they were carriers either before or by the time they were in high school.

Ninety-three percent (26/28) of the women wished they had known that they were carriers prior to becoming involved in a serious relationship. When asked for their reasons, common responses were: "Would have wanted to discuss it (risk) so that a decision would have been informed and mutual" or "Would have married someone willing not to have children."

When asked at what age they felt a daughter should first learn that fra(X) syndrome is inherited and she could have an affected child, the mean was 12.9 years (SD 3.9) (Fig. 2). The mean age indicated for having carrier testing done was 9.86 years (SD 6.23) (Fig. 3). The women were asked the same question in relationship to sons. They were reminded prior to responding that the risk for transmitting males is for affected grandchildren. The mean age given for learning that fra(X) syndrome is inherited was 12.8 years (SD 3.78) and a mean age of 10.6 years (SD 6.1) for carrier testing. The mean age for carrier testing in both daughters and sons is lower than that given for the age for informing of the genetic risk, as 46% (13/28) of the women would test at a younger age than they would tell the child the results of the test.

The women who felt that a child should not know of his/her carrier status until over the age of 16 years felt that knowledge of carrier status was "Something which must be dealt with, but not something you need to burden a child with." For those who would test and tell younger than 16 years, the responses from the follow up questions demonstrated a desire to gradually introduce the information and to make plans. Examples of those responses were: "Tell early so you don't spring it on her when she is older"; "Able to plan/know more about the risk of what could happen and have more time to make choices; Age 12–15 years is old enough to start thinking about a family"; "Test young because it is easier to accept"; and "Should always know, part of who you are and is nothing to be ashamed of." For those women who would test at a younger age than they would report the results the reasons given were: "Test young to know if you need to tell"; "To prepare for what is coming"; and "Fear of the unknown, face it and make plans."

Trends in the responses were identified in how the women felt about their own carrier status. Women who responded that they felt this information should be given when a child is over the age of 16 years were more negative in their responses on how they viewed themselves since learning of their carrier status ($P = 0.003$) and reported greater levels of emotional upset related to their current feelings about being a carrier than women who responded that they felt this information should be known before the age of 16 years. Although the women who wished they had known prior to the age of 16 years viewed themselves in a more positive manner, they viewed the risk for affected offspring higher than those women who would delay transmitting this information until older than age 16 years ($P = 0.055$).

There was also a direct relationship to the age preferred for carrier testing and informing for themselves and those stated for their children. Women who would have liked to have been informed/tested under the age of 16 years responded in a similar manner for daughters to have carrier testing ($P = 0.001$) and knowledge of the genetic risk ($P = 0.023$) and for their sons to have carrier testing ($P = 0.004$). There was no relationship identified regarding the actual age of the woman and the age she felt her children should be informed and tested.

Attitude About Marital/Family Relationships

Sixty-four percent (18/28) felt that their relationship with their husband had changed as a result of the diagnosis and their carrier status. The responses on the VAS with a mean of 5.7 (SD 2.35) indicates that the change was felt overall to be a slight improvement, with 72% (13/18) indicating a positive change and 27% (5/18) a negative change. The comments made indicates that if the change was positive an increase in understanding and communication was the basis for it. For example, "Not knowing what was wrong was horrendous; both of us tried to figure out what happened." However, if a negative response was indicated, this was based on feelings that their spouse blamed them as the cause of their child being affected.

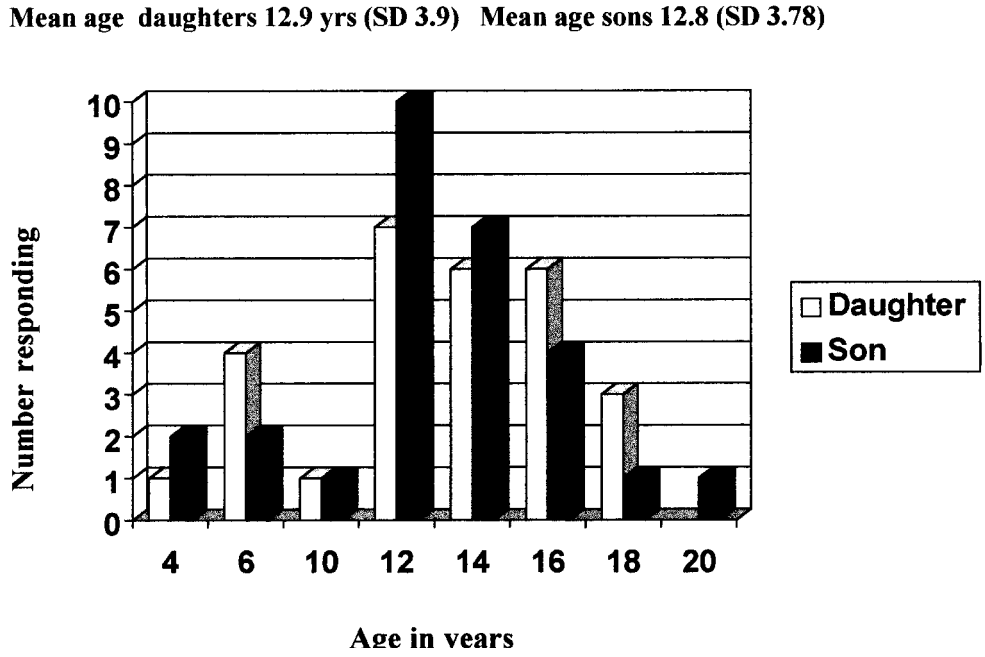

Fig. 2. At what age should children be told of the inheritance of fra(X) syndrome?

Learning that fra(X) syndrome was in the family and relatives were at an increased risk for having affected children was reported to have been upsetting with a mean on the VAS of 4.3 (SD 2.75). Sixty percent (17/28) felt that there had been an improvement in their relationships with their sibs with a mean of 6.4 (SD 1.69) on the VAS with only one woman reporting a negative response. When asked about relationships with relatives, 43% (12/28) felt there had been a change with a mean of 5.57 (SD 1.70) on the VAS. The positive and negative responses were equally divided. For both sibs and relatives improvement in relationships were felt to have occurred if the response to the diagnosis was a positive one, but a response that was negative caused a

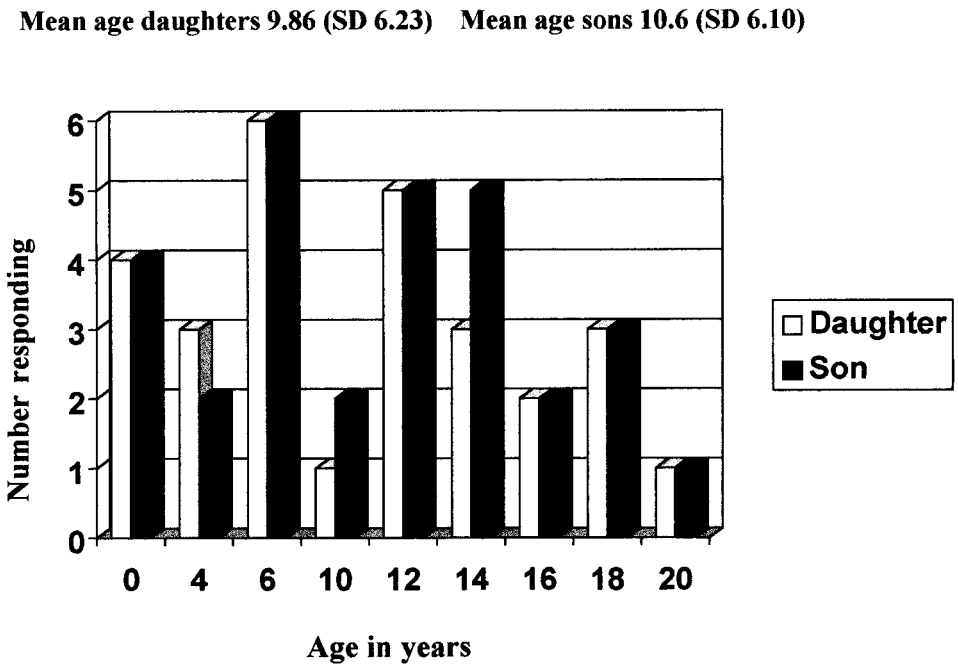

Fig. 3. At what age should carrier testing be done for fra(X) syndrome?

deterioration in the relationship. A reaction was considered negative by the woman if the relative either refused to be tested or to believe that fra(X) syndrome was in the family.

All felt that sibs and relatives should be told about the inheritance of fra(X) syndrome and the genetic risk so that informed decisions could be made regarding reproduction and so that the educational needs of the affected individuals in the family could be better met. Seventy-five percent (21/28) felt that the information should first be given by a relative, with follow-up by a genetic counselor or physician with the remaining 25% told directly by a genetic counselor or physician.

DISCUSSION

In this study strong trends were identified regarding the attitude and opinion of carriers of the fra(X) syndrome about carrier testing and the impact of fra(X) syndrome on their lives. Fra(X) syndrome was viewed as a very serious problem and the risk to offspring high. Although the numeric risk response did not differ significantly, a trend was noted that the perceived risk for having an affected daughter was lower than for an affected son. The risk responses tended to be based on their own experiences with fra(X) syndrome and on the inheritance of the maternal X chromosome without regard to the paternal contribution. Women who wished they had knowledge of their carrier status before they were 16 years of age viewed the risk of affected children as significantly higher than women who would have delayed carrier knowledge until older than 16 years. They reported that prior knowledge of carrier status would have changed their reproductive plans, indicating that they would have either reduced the size of their families or not had biological children. All felt that relatives should be informed about the inheritance of fra(X) syndrome, with the majority feeling that the information should first be given by an individual known to the relative with follow-up by a genetic counselor or physician.

Studies designed to evaluate the impact of carrier testing on self-esteem and self image have used recessively inherited conditions such as Tay-Sachs, sickle cell, or cystic fibrosis as models. In these studies, a range of feelings and emotions that may be associated with carrier testing have been identified. These include hostility, anxiety, depression, stigma, shock, denial, upset, blame, guilt, anger, shattered body image, lowered self-concept, feelings of reduced desirability as a mate, questions of parental capacity, and fear of disclosure [Childs et al., 1976; Kessler et al., 1984; Watson et al., 1992; Kenen and Schmidt, 1978; Marteau et al., 1992]. Most of the women in this study reported that learning they were carriers had changed the way they viewed themselves. They related that although they did not feel guilty about being a carrier, they did have feelings of anger, depression, or lowered self esteem related to having an affected child. Those who felt the change had been a positive one indicated that there was relief in knowing what had caused the disability in their children and they felt they now understood themselves better.

The majority of the women interviewed felt that the age to inform their children of the inheritance of fra(X) was 12 years and the optimal timing for carrier testing was 10 years. These women felt that the information should be introduced gradually, in an age appropriate manner, but that this information should be known and understood prior to the possibility of sexual activity. Those women who preferred testing at a young age, but would delay informing their children of the results until the preteen/teenage years, indicated that the reason for this was so they would know if they needed to prepare their children for ultimately learning they were carriers. They also felt they would be better prepared to identify possible school or behavioral problems associated with female carriers of the full mutation. The women interviewed stated that growing up with knowledge of their carrier status would have been preferable to learning this information as adults, and they endorsed an aggressive approach to informing and testing their children. However, as the women in this study all have personal experience with the clinical problems of the fra(X) syndrome the responses may be biased toward this group and may not apply to naive populations.

Correlations between the responses to age of carrier testing and feelings related to their own carrier status were identified. There was a direct relationship between the responses regarding when they themselves would have wished to have known their carrier status and the age response given for their children. The women who responded with a younger age for informing about the genetic risk and testing offspring report significantly more positive feelings about their own carrier status than women who felt the information should be given after the age of 16 years. This trend was true for their responses relating to how they felt when they initially found out they were carriers and their current feelings related to being a carrier.

Carrier testing in minors is controversial. There have been several recent position papers containing age recommendations for carrier testing. The American Society of Human Genetics/American College of Medical Genetics has recently published a points-to-consider paper opposing carrier testing in children unless clear benefits can be demonstrated and the child meets conditions of "competence, voluntariness, and adequate understanding of the information" [ASHG/ACMG, 1995]. The National Society of Genetic Counselors [NSGC, 1995] newly adopted policy addresses the issue of prenatal and childhood testing for adult-onset disorders, but does not address carrier testing in children. Both papers emphasize the need for age-appropriate genetic counseling and the need for further research into the psychological consequences of testing in children and adolescents. The report of the Clinical Genetics Society (UK) opposed carrier testing in children for the purposes of making reproductive decisions [Clarke et al., 1994]. Although they opposed carrier testing, they felt that families should discuss the genetic risk with younger children, but not perform testing until an individual was an autonomous adult. In all of these papers concerns were raised about potential harm as a

result of carrier testing which include damage to self-esteem, distortion of the family's perception of the child, loss of future adult autonomy and confidentiality, discrimination (insurance, employment, or education), and adverse effects on the capacity to form future relationships. These reports also acknowledge there may be some benefits to testing young. The arguments for testing young include: enhancing communication within the family allowing for the child to adjust to the genetic risk, resolution of parental concerns about carrier status, and ensuring that the entire family is tested. The guideline presented by Wertz et al. [1994] regarding carrier testing in minors states that testing can be done, but only with full informed consent of the minor and that it should be limited to situations where the risk is high. Wertz et al. endorsed the concept of early disclosure of genetic risk, so that individual coping mechanisms can be developed, with testing done later.

Guidelines have been well developed for presymptomatic testing for Huntingtons Disease [Huntingtons Disease Association, 1994] and for population screening for cystic fibrosis [Cystic Fibrosis NIH Workshop, 1990]. The genetic counseling, education about the ramifications of testing, and follow-up services which are important components of these guidelines would also be expected to be requirements for the basis of guidelines for carrier testing in fra(X) syndrome. Results of this study suggests that some concepts inherent in the Huntingtons and cystic fibrosis guidelines regarding timing of testing and informing of carrier status may not be generalizable to families with fra(X) syndrome as carriers of fra(X) syndrome face the risk for having an affected child; they are not at risk for developing a debilitating disease themselves. In addition, the risk associated with being a carrier of a recessive disorder is based on the carrier status of both partners. The reproductive risk associated with fra(X) syndrome is present regardless of the partner's status.

Fra(X) families raising daughters and sons who have been identified prenatally as carriers and the daughters of transmitting males are currently facing difficult decisions regarding when and how to inform their children about the genetic risk without direct carrier testing being done. In addition, children are being tested because of educational concerns. As our sample size was small and only included women with personal experience with fra(X) syndrome the data from this study should be interpreted with caution. Further investigation is needed to determine the psychological consequences of carrier testing specifically for fra(X) syndrome in order to assist in providing information and genetic counseling for families with fra(X) syndrome facing these difficult issues.

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